

Antiangiogenic therapy may offer several advantages over conventional chemotherapy for the treatment of cancer.

Antiangiogenic agents have low toxicity in preclinical  
5 trials and development of drug resistance has not been  
observed (Folkman, J., *Seminars in Medicine of the Beth  
Israel Hospital, Boston* 333(26): 1757-1763, 1995). As  
angiogenesis is a complex process, made up of many steps  
including invasion, proliferation and migration of  
10 endothelial cells, it can be anticipated that  
combination therapies will be most effective. Kumar and  
Armstrong describe anti-angiogenesis therapy used as an  
adjunct to chemotherapy, radiation therapy, or surgery.  
(Kumar, CC, and Armstrong, L., Tumor-induced  
15 angiogenesis: a novel target for drug therapy?, *Emerging  
Drugs* (1997), 2, 175-190).

The phrase "therapeutically-effective" is intended  
to qualify the amount of each agent that will achieve  
the goal of improvement in neoplastic disease severity  
20 and the frequency of neoplastic disease over treatment  
of each agent by itself, while avoiding adverse side  
effects typically associated with alternative therapies.

A "therapeutic effect" or "therapeutic effective  
amount" is intended to qualify the amount of an  
25 anticancer agent required to relieve to some extent one  
or more of the symptoms of a neoplasia disorder,  
including, but is not limited to: 1) reduction in the  
number of cancer cells; 2) reduction in tumor size; 3)  
inhibition (i.e., slowing to some extent, preferably  
30 stopping) of cancer cell infiltration into peripheral  
organs; 3) inhibition (i.e., slowing to some extent,  
preferably stopping) of tumor metastasis; 4) inhibition,

to some extent, of tumor growth; 5) relieving or reducing to some extent one or more of the symptoms associated with the disorder; and/or 6) relieving or reducing the side effects associated with the administration of anticancer agents.

The phrase "combination therapy" (or "co-therapy") embraces the administration of a cyclooxygenase-2 inhibitor and an antineoplastic agent as part of a specific treatment regimen intended to provide a beneficial effect from the co-action of these therapeutic agents. The beneficial effect of the combination includes, but is not limited to, pharmacokinetic or pharmacodynamic co-action resulting from the combination of therapeutic agents.

Administration of these therapeutic agents in combination typically is carried out over a defined time period (usually minutes, hours, days or weeks depending upon the combination selected). "Combination therapy" generally is not intended to encompass the administration of two or more of these therapeutic agents as part of separate monotherapy regimens that incidentally and arbitrarily result in the combinations of the present invention. "Combination therapy" is intended to embrace administration of these therapeutic agents in a sequential manner, that is, wherein each therapeutic agent is administered at a different time, as well as administration of these therapeutic agents, or at least two of the therapeutic agents, in a substantially simultaneous manner. Substantially simultaneous administration can be accomplished, for example, by administering to the subject a single capsule having a fixed ratio of each therapeutic agent

or in multiple, single capsules for each of the therapeutic agents. Sequential or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, oral routes, intravenous routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination selected may be administered by intravenous injection while the other therapeutic agents of the combination may be administered orally. Alternatively, for example, all therapeutic agents may be administered orally or all therapeutic agents may be administered by intravenous injection. The sequence in which the therapeutic agents are administered is not narrowly critical. "Combination therapy" also can embrace the administration of the therapeutic agents as described above in further combination with other biologically active ingredients (such as, but not limited to, a second and different antineoplastic agent) and non-drug therapies (such as, but not limited to, surgery or radiation treatment). Where the combination therapy further comprises radiation treatment, the radiation treatment may be conducted at any suitable time so long as a beneficial effect from the co-action of the combination of the therapeutic agents and radiation treatment is achieved. For example, in appropriate cases, the beneficial effect is still achieved when the radiation treatment is temporally removed from the administration of the therapeutic agents, perhaps by days or even weeks.